Remarks/Arguments

This response is being filed within the shortened three-month statutory period for responding to the final office action that was mailed on April 29, 2004. Therefore, no petition and fee for an extension of time are enclosed herewith.

Claims

Claims prior to this amendment are referred to as "currently pending" claims. This response amends currently pending Claims 3 and 7. After amendment this application will have one independent Claim (currently pending Claim 1) and a total of 10 Claims (currently pending Claims 1-2, 4-6, 8-10 and currently amended Claims 3 and 7). Applicants previously paid for up to 20 total Claims and three independent Claims. Therefore, no fee for excess Claims is enclosed with this response.

Specification

In item 2 on page 2 of the outstanding Office Action, the Examiner objects to pages 25 and 29 of the specification because no sequence I.D. numbers are given. This objection should be withdrawn because we filed on November 30, 2001 a response that amends pages 25 and 29 of the specification to include these sequence I.D. numbers. The response was filed via U.S. Express Mail with a Certificate of Mailing dated November 30, 2001.

Claim Rejection – 35 U.S.C. § 112, first paragraph

The Examiner rejects Claims 1-10 in item 3 on page 2 of the Office action and asserts that the specification does not reasonably provide enablement for a non-covalent glycoconjugate of a polysaccharide and a polypeptide, where the structure of polysaccharide, the sequence of the polypeptide comprising SEQ ID NO: 1 and the molar ratio of the polysaccharide to the polypeptide are not defined.

Applicants traverse the Examiner's rejection. Applicants submit that Claim 1 claims "a glycoconjugate formed by non-covalent association of a polysaccharide with a polypeptide" and recites the claim limitations of Claim 1. Applicants submit that Claim 1 enables a person with ordinary skill in the art to make and use the invention without undue experimentation.

As explained below, a person skilled in the art who reads the specification would be able to make and use the invention without undue experimentation. For example on page 19, lines 6 to 24 describe a method of formation of polysaccharide polypeptide conjugates. There is described from line 5 to line 24 one method, which enables a person skilled in the art to make and use the claimed invention. It is mentioned therein that the polysaccharide polypeptide conjugates can be within the 1/1 to 1/19 mol/mol range. This range is clearly a preferred range. The specification enables the person skilled in the art to make a polysaccharide polypeptide conjugate. Further, the specification discloses in Example 1 (item 3 on page 25), Example 2 (item 3 on page 29) and Example 3 (item 3 on page 32) how to make the claimed product. This disclosure enables a person skilled in the art to make the claimed glycoconjugate without undue experimentation. It is believed that the specification provides enablement for the person skilled in the art to make and use the invention of currently pending Claim 1. Therefore, it is believed that currently pending Claim 1 is allowable.

Currently pending Claim 2 recites a mol/mol relation between the two polypeptides between 1/3 and 3/1. The specification provides support for Claim 2 in lines 31-32 on page 19. The Examiner's rejection of the Claims based on the assertion that the specification does not provide enablement for a non-covalent glycoconjugate where the molar ratios are not defined, is respectfully traversed in view of currently pending Claim 2. Claim 2 recites a molar ratio, which is supported by the specification as mentioned above.

Currently pending Claim 3 was amended to be dependent from currently pending Claim 2. Amended Claim 3 should be allowable because it is dependent

from Claim 2, which recites a molar ratio. The specification provides enablement for amended Claim 3. A person skilled in the art is able to make and use the invention as recited in Claim 3, which is dependent from Claim 2, especially because Claim 2 recites the molar ratio.

Currently pending Claim 7 was amended to be dependent from currently pending Claim 3. Currently pending Claims 8 and 10 are dependent from currently amended Claim 3. Since all the dependent claims are either directly or indirectly dependent from Claim 1, it is believed that the dependent claims overcome the rejection under 35 U.S.C. § 112, paragraph 1 as well.

Claim Rejection – 35 U.S.C. § 112, second paragraph

In item 4 on page 7 of the Office Action, the Examiner rejects Claims 5 and 8 under 35 U.S.C. § 112, second paragraph for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that the applicants regard as the invention. The Examiner rejects Claims 5 and 8 because of the term "to treat disorders of an immunological system related to a higher production of tumor necrosis factor (TNF)".

Applicants respectfully traverse the rejection and submit that it is believed a person skilled in the art would be aware of the particular immunological disorders that relate to higher production of TNF.

Applicants submit annex 1, which includes a list of immunological/ inflammatory disorders related to higher production of tumor necrosis factor (TNF), which eventually could be treated with the pharmacologically active polypeptide glycoconjugates of the claimed invention. The listed diseases are documented in the literature as shown in annex 1.

Applicants further submit annex 2, which indicates the reference point for "higher production of TNF". Annex 2 shows that a person skilled in the art is familiar with such a well-known expression in the art as "higher production of TNF" and a reference point for comparison is documented in the literature.

In view of the foregoing, the rejection of currently pending claims 5 and 8 should be withdrawn.

Reconsideration and examination of the present application as amended is respectfully requested. The application is now in condition for allowance. Allowance of the application at an early date is respectfully requested.

Applicants reserve the right to seek protection for any unclaimed subject matter, either subsequently in the prosecution of the present case or in a divisional or continuation application.

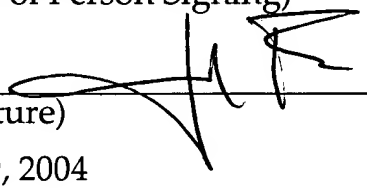
This response amends currently pending Claims 3 and 7. The amendments that are described in the preceding sentence were done to improve the wording of the claims and/or to more fully claim the Applicant's invention and were not done to overcome the prior art, were not done to overcome rejections under 35 U.S.C. § 112, and were not done to overcome any other rejections or objections. The amendments that are described in the first sentence of this paragraph shall not be considered necessary to overcome the prior art, shall not be considered necessary to overcome rejections under 35 U.S.C. § 112, and shall not be considered necessary to overcome any other rejections or objections.

The Commissioner is authorized to charge any additional fees, which may be required or credit overpayment to deposit account no. 12-0415. In particular, if this response is not timely filed, then the Commissioner is authorized to treat this response as including a petition to extend the time period pursuant to 37 CFR 1.136 (a) requesting an extension of time of the number of months necessary to make this response timely filed. The petition fee due in connection therewith may be charged to deposit account no. 12-0415.

I hereby certify that this correspondence with all of the indicated enclosures is being deposited with the United States Postal Service with sufficient postage as first-class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Arlington, VA 22313-1450 on

July 29, 2004
(Date of Deposit)

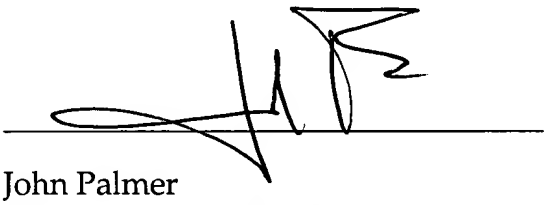
John Palmer
(Name of Person Signing)



(Signature)

July 29, 2004
(Date)

Respectfully submitted,



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Enclosures: Annex 1 and Annex 2

Annex 1

List of immunological/inflammatory disorders related to higher production of TNF susceptible of being treated with the polypeptide glyconconjugates of the instant invention

Inflammatory liver disease

Hepatitis B

- Spengler U, Zachoval R, Gallati H, Jung MC, Hoffmann R, Riethmuller G, Pape G. Serum levels and in situ expression of TNF-alpha and TNF-alpha binding proteins in inflammatory liver diseases. Cytokine. 1996 Nov;8(11):864-72.
- Wang JY, Liu P. Abnormal immunity and gene mutation in patients with severe hepatitis-B. World J Gastroenterol. 2003 Sep;9(9):2009-11.

Alcoholic Hepatitis

- Lieber CS. New concepts of the pathogenesis of alcoholic liver disease lead to novel treatments. Curr Gastroenterol Rep. 2004 Feb;6(1):60-5
- Mookerjee RP, Sen S, Davies NA, Hodges SJ, Williams R, Jalan R. Tumour necrosis factor alpha is an important mediator of portal and systemic haemodynamic derangements in alcoholic hepatitis. Gut. 2003 Aug;52(8):1182-7.
- Tilg H, Jalan R, Kaser A, Davies NA, Offner FA, Hodges SJ, Ludwiczek O, Shawcross D, Zoller H, Alisa A, Mookerjee RP, Graziadei I, Datz C, Trauner M, Schuppan D, Obrist P, Vogel W, Williams R. Anti-tumor necrosis factor alpha monoclonal antibody therapy in severe alcoholic hepatitis. J Hepatol. 2003 Apr;38(4):419-25.
-McClain CJ, Barve S, Barve S, Deaciuc I, Hill DB. Tumor necrosis factor and alcoholic liver disease. Alcohol Clin Exp Res. 1998 Aug;22(5 Suppl):248S-252S.
- Naveau S, Emilie D, Balian A, Grangeot-Keros L, Borotto E, Portier A, Giraud V, Capron F, Galanaud P, Chaput JC. Plasma levels of soluble tumor necrosis factor receptors p55 and p75 in patients with alcoholic liver disease of increasing severity. J Hepatol. 1998 May;28(5):778-84.

Inflammatory bowel disease

- Gonzalez S, Rodrigo L, Martinez-Borra J, López-Vazquez A, Fuente Nino P, Cadahia V, Saro C, Dieguez MA, Lopez-Larrea C. TNF-alpha –308A promoter polymorphism is associated with enhanced TNF-alpha production and inflammatory activity in Crohn's patients with fistulizing disease. Am J Gastroenterol 2003 May;98(5):1101-6.
- Nahar IK, Shojania K, Marra CA, Alamgir AH, Anis AH. Infliximab treatment of rheumatoid arthritis and Crohn's disease. Ann Pharmacother. 2003 Sep;37(9):1256-65.
- Waetzig GH, Seegert D, Rosentiel P, Nikolaus S, Schreiber S. P38 mitogen-activated protein kinase is activated and linked TNF-alpha signaling in inflammatory bowel disease. J Immunol. 2002 May 15;168(10):5342-51.

Chronic obstructive pulmonary disease

- Thomas PS, Yates DH, Barnes PJ. Tumor necrosis factor-α increases airway responsiveness and sputum neutrophilia in normal human subjects. Am J Respir Crit Care Med 1995; 152:76-80.

- Takabatake N, Nakamura H, Inoue S, Terashita K, Yuki H, Kato S, Yasumura S, Tomoike H. Circulating levels of soluble Fas ligand and soluble Fas in patients with chronic obstructive pulmonary disease. Respir Med. 2000 Dec;94(12):1215-20.

Psoriasis y psoriatic arthritis

- Victor FC, Gottlieb AB, Menter A. Changing paradigms in dermatology: tumor necrosis factor alpha (TNF-alpha) blockade in psoriasis and psoriatic arthritis. Clin Dermatol. 2003 Sep-Oct;21(5):392-7.
- Gottlieb AB. Infliximab for psoriasis. J Acad Dermatol 2003 Aug;49(2 suppl):S112-7.
- Nahar IK, Shojania K, Marra CA, Alamgir AH, Anis AH. Infliximab treatment of rheumatoid arthritis and Crohn's disease. Ann Pharmacother. 2003 Sep;37(9):1256-65.
- Reimold AM. New indications for treatment of chronic inflammation by TNF-alpha blockade. Am J Med Sci. 2003 Feb;325(2):75-92.

Spondiloarthritis/rheumatoid arthritis

- Neale ML, Williams BD, Matthews N. Tumor necrosis factor activity in joint fluids from rheumatoid arthritis patients. Br J Rheumatol 1989; 28:104-108.
- Bucala R. Ritchlin C, Winchester R. Cerami A. Constitutive production of inflammatory and mitogenic cytokines by rheumatoid synovial fibroblasts. J Exp Med 1991; 173:569-574.
- Müsssener A, Klareskog L, Lorentzen JC, Kleinau S. TNF-α dominates cytokine mRNA expression in lymphoid tissues of rats developing collagen- and oil-induced arthritis. Scand J Immunol 1995; 42:128-134.
- Bush KA, Kirkham BW, Walker JS. The in vivo effects of tumour necrosis factor blockade on the early cell mediated immune events and syndrome expression rat adjuvant arthritis. Clin Exp Immunol. 2002 Mar;127(3):423-9.
- Hassan AB et al. J Autoimmunity 1998; 11(5): 503-508

Chronic fatigue syndrome

- Sarma R, Anker SD. Cytokines, apoptosis and cachexia: the potential for TNF antagonism. Int J Cardiol. 2002 Sep; 85(1):161-71
- Patarca R. Cytokines and chronic fatigue syndrome. Ann N Y Acad Sci. 2001 Mar;933:185-200.

Cancer/Cachexia/Hematological disorders

- Aderka D, Fisher S, Levo Y, Holtmann H, Hahn T, Wallach O. Cachectin/tumour-necrosis-factor production by cancer patients [letter]. Lancet 1985; 2:1190.
- Balkwill F, Osborne R, Burke F, et al. Evidence for tumour necrosis factor/cachectin production in cancer. Lancet 1987; 2:1229-1232.
- Younes A, Aggarwall BB. Clinical implications of the tumor necrosis factor family in benign and malignant hematologic disorders. Cancer. 2003 Aug 1;98(3):458-67.
- Alexandrakis MG, Passam FH, Sfiridaki K, Moschandrea J, Pappa C, Liapi D, Petreli E, Roussou P, Kyriakou DS. Interleukin-18 in multiple myeloma patients: serum levels in relation to response to treatment and survival. Leukemia Res 2004; 28(3): 259-266
- Visentainer JE, Lieber SR, Persoli LB, Vigorito AC, Aranha FJ, de Brito Eid KA, Oliveira GB, Miranda EC, de Souza CA. Serum cytokine levels and acute graft-versus-host disease after HLA-identical hematopoietic stem cell transplantation. Exp Hematology 2003; 31(11): 1044-1050

Septic shock and systemic inflammatory response syndrome (SIRS)

- Tracey KJ, Beutler B, Lowry SF, et al. Shock and tissue injury induced by recombinant human cachectin. Science 1986; 234:470-474.
- Tracey KJ, Fong Y, Hesse DG, et al. Anti-cachectin/TNF monoclonal antibodies prevent septic shock during lethal bacteraemia. Nature 1987; 330:662-664.
- Marano MA, Fong Y, Moldawer LL, et al. Serum cachectin/TNF in critically ill patients with burns correlates with infection and mortality. Surg Gynecol Obstet 1990; 170:32-38.
- Groeneveld PH, Kwappenberg KM, Langermans JA, Nibbering PH, Curtis L. Relation between pro- and anti-inflammatory cytokines and the production of nitric oxide (NO) in severe sepsis. Cytokine 1997; 9(2): 138-142.
- Rodriguez-Gaspar M, Santolaria F, Jarque-Lopez A, Gonzalez-Reimers E, Milena A, de la Vega MJ, Rodriguez-Rodriguez E, Gomez-Sirvent JL.Prognostic value of cytokines in SIRS general medical patients. Cytokine 2001; 15(4):232-236

Vasculitis

- Gonzalez-Gay MA, Amoli MM, Garcia-Porrua C, Ollier WE. Genetic markers of disease susceptibility and severity in giant cell arteritis and polymyalgia reumática. Semin Arthritis Rheum. 2003 Aug; 33(1): 38-48.
- Elezoglou AV, Sfikakis PP, Vaiopoulos G, Kapsimali V, Kaklamanis PG. Serum levels of soluble TNF-alpha receptor-II (P75), circulating gammadelta T-cells and Adamantiades-Behcet's disease activity. Adv Exp Med Biol. 2003; 528: 261-5.
- Chien YH, Chang KW, Yang YH, Lu MY, Lin YT, Chiang BL. Association between levels of TNF-alpha and TNF-alpha promoter -308 A/A polymorphism in children with Kawasaki disease. J Formos Med Assoc. 2003 Mar; 102(3): 147-50.

Malaria

- McGuire W, Hill AVS, Allsopp CEM, Greenwood BM, Kwiatkowski D. Variation in the TNF-α promoter region associated with susceptibility to cerebral malaria. Nature 1994; 371:508-511.
- Kwiatkowski D, Hill AVS, Sambou I, et al. TNF concentration in fatal cerebral, non-fatal cerebral, and uncomplicated Plasmodium falciparum malaria. Lancet 1990; 336:1201-1204.

Meningitis/encephalitis

- Waage A, Halstensen A, Shalaby R, Brandtzaeg P, Kierulf P, Espevik T. Local production of tumor necrosis factor-alpha, interleukin 1, and interleukin 6 in meningococcal meningitis. J Exp Med 1989; 170:1859-1967.
- Marceline van Furth A, Seijmonsbergen EM, Langermans JAM, Groeneveld PHP, De Bel CE, Van Furth R. High levels of interleukin 10 and tumor necrosis factor α in cerebrospinal fluid during the onset of bacterial meningitis. Clin Infect Dis 1995; 21:220-222.

Multiple sclerosis

- Selmaj K, Raine CS, Cannella B, Brosnan CF. Identification of lymphotoxin and tumor necrosis factor in multiple sclerosis lesions. J Clin Invest 1991; 87: 949-954.

AIDS

- Folks TM, Justement J, Kinter A, Dinarello CA, Fauci AS. Cytokine-induced expression of HIV-1 in a chronically infected promonocyte cell line. Science 1987; 238:800-802.

- Griffin GE, Leung K, Fols TM, Kunkel S, Nabel GJ. Activation of HIV gene expression during monocyte differentiation by induction of NF-kappa B. Nature 1989; 339:70-73.
- Osborn L, Kunkel S, Nabel GJ. Tumor necrosis factor alpha and interleukin 1 stimulate the human immunodeficiency virus enhancer by activation of the nuclear factor kappa B. Proc Natl Acad Sci USA 1989; 86:2336-2340.

ANNEX 2

Point of reference for "higher production of TNF"

Pathology	Method employed	TNFa* (n)	TNFa* in controls (n)	Reference
Multiple myeloma				
stadio I	ELISA	13.8 ± 2.6 pg/ml (15)	12.6 ± 3.9 pg/ml (25)	M. G. Alexandrakis et al, Leukemia Research, 28(3), 2004, 259-266
stadio II		18.8 ± 5.2 pg/ml (23)		
stadio III		31.4 ± 10.3 pg/ml (27)		
Acute disease of graf against host alter transplantation of stem cells with identical HLA				
Absence of acute rejection	ELISA	70.2 ± 10.9 pg/ml (8)		Jeane Eliete Laguila Visentainer et al, Experimental Hematology, 31 (11), 2003, Pages 1044-1050
Presence of acute rejection		71.9 ± 9.8 pg/ml (5)		
In systemic inflammatory response sindrome (SIRS)				
SIRS	Chemiluminiscence enzyme immunimetric assay	16.7 ± 1.0 pg/ml (103)	10.5 ± 0.7 pg/ml (19)	Melchor Rodríguez-Gaspar et al, Cytokine, 15(4) 2001, Pages 232-236
Sepsis		18.7 ± 2 pg/ml (40)		
Severe sepsis and septic shock		48.4 ± 17 pg/ml (21)		
Severe sepsis	ELISA	7 range 0-50 pg/ml (23)		Paul H. P. Groeneveld et al, Cytokine, 9(2) 1997, Pages 138-142
In mixed connective tissue disease (MCTD)		8.8 (22)	0.4 (21)	
Systemic erythematoso lupus	ELISA	0.8 (21)		Adla Bakri Hassan et al, Journal of Autoimmunity, 11(5)1998, Pages 503-508
Reumatoid artritis		3.1 (22)		

* Expressed as mean and SD or range

This table shows different examples of pathologies related to high serum TNF levels as well as the corresponding levels in healthy controls